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(21) International Application Number: PCT/EP97/00558 (22) International Filing Date: 5 February 1997 (05.02.97) (30) Priority Data: MI96A000239 8 February 1996 (08.02.96) IT (71) Applicant (for all designated States except US): GIULIANI S.A. [CH/CH]; Via Riviera, 21, CH-6976 Castagnola (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): GOOSSENS, Herman [BE/BE]; Boterberg 10, B-1730 Bekkerzeel-Asse (BE). FRIGERIO, Giuliano [IT/IT]; Viale L. Einaudi, 15/G, I-20020 Arese (IT). (74) Agents: APPOLONI, Romano et al.; Ing. Barzano' & Zanardo, Milano S.p.A., Via Borgonuovo, 10, I-20121 Milano (IT).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS FOR BIOLOGICAL TREATMENT OF INFECTIONS BY ENTEROCOCCUS FAECIUM STRAINS RESISTANT TO ANTIBIOTICS AND TO VANCOMYCIN IN PARTICULAR (VRE) (57) Abstract The present invention relates to the use of an <i>Enterococcus faecium</i> strain for preparing a medicinal product suitable for the therapeutical treatment of infections, with particular reference to enterocolites, supported by <i>Enterococcus faecium</i> strains resistant to antibiotics and in particular, vancomycin, the so-said "VRE" strains. In particular, <i>Enterococcus faecium</i> is taken into consideration and disclosed which belongs to that strain referred to as "SF68". The invention also discloses and relates to pharmaceutical compositions for such a use.		

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"Pharmaceutical compositions for biological treatment of infections by Enterococcus faecium strains resistant to antibiotics and to vancomycin in particular (VRE)"

5 Italian patent No. 1,112,479 in the name of Giuliani S.A. relates to a pharmaceutical composition which is particularly suitable for treating enteritides and infective diarrhoeas in general, characterized in that, as its active
10 principle, it contains a culture of bacteria belonging to Enterococcus faecium species.

In particular, said patent relates to compositions in which bacteria of Enterococcus faecium species are used which belong to SF68
15 bacterial strain.

SF68 bacterial strain is the active principle of the patent medicine BIOFLORIN®, a well-documented biological preparation containing this particular strain of Enterococcus faecium in dry form, widely
20 used for treating acute diarrhoeal enterocolitis forms.

Since 1984, Enterococcus faecium, formerly classified within the family of Streptococcaceae, Streptococcus genus of Lancefield's D group, has been
25 considered as belonging to Enterococcus genus, and appears as being a gram +, aerobic, facultative anaerobic, non-sporigenous, non-mobile spherical coccus of approximately 1 μ of diameter, generally forming variously long chains of cells.

30 The optimal growth temperature is of 36-37°C,

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and the optimal growth pH value is 7. The particularly suitable culture media for an optimal growth are MRS broth (Difco) and horse blood agar. The growth can be estimated from a uniform turbidity
5 in liquid media and the formation of small round, slightly convex, smooth colonies on solid media. On colonies growing in blood agar a slight α -hemolysis can be observed.

In blood TSA agar (Difco) with 5% rabbit, sheep
10 and human and Guinea pig and horse red cells, an α -hemolysis is obtained in the presence of horse, sheep and human blood, not in the presence of rat, rabbit and Guinea pig blood.

SF68 strain was originally isolated from human
15 organisms and was also used in food industry, in particular for cheese fermentation.

SF68 strain was deposited by Giuliani Company with the DSM (Deutsche Sammlung Mikroorganismen und Zellkulturen): the accession code is DSM 8912.

20 The Enterococcus faecium SF68 containing preparation for clinical use was developed in 1978; the same strain was also studied and used in veterinary field.

Giuliani Company developed their preparation
25 during 1978-1980, through a very large amount of toxicological, microbiological and clinical studies; nearly all of the latter were carried out as controlled double-blind vs. placebo or vs. active control studies.

30 The survey by Loizeau E. (published on "Revue

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Médicale de la Suisse Romande" 114; 651, 1994) summarizes the biological and clinical properties of the preparation.

Recently, Campylobacter Spp., Helicobacter Spp.
5 and vancomycin-resistant enterococci (VRE) became very important in clinical gastroenterological microbiology due to several reasons:

- Campylobacter Spp. because they proved to be the enteropathogenic bacteria more frequently observed
10 in infective intestinal pathology; on the contrary, the most frequent cause in absolute is represented by rotaviruses;
- Helicobacter pilori because they are frequently involved in etiopathogenesis of peptic ulcer
15 disease;
- VRE (vancomycin-resistant) enterococci because they are very often implied in nosocomial emergencies (nosocomial or hospital infections) with a high potential of morbidity and mortality,
20 as observed from important epidemiological studies performed in the U.S.A. and Europe.

In our era, characterized by the consumption of large amounts of antibiotics and the considerable increase in germs resistant to many of said so
25 widely used antibiotics, exploring the potential of biological products capable of producing bacteriocins or, anyway, biologically active substances against pathogenic agents appears of considerable interest.

30 It seems useful to us reminding here that

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Enterococcus faecium SF68 strain already demonstrated a considerable antagonist activity against several enteropathogenic germs, among which Salmonellae, Coli, Shigellae and still other
5 bacteria. SF68 strain had also shown antagonist activity against some viruses causing intestinal infections.

Recent studies have demonstrated an inhibiting and bactericidal activity of Enterococcus faecium
10 SF68 strain against a large number of types of Campylobacter, whereas rather low resulted to be the activity against Helicobacter pilori.

We have now surprisingly found, and this is the subject-matter of the present invention, together
15 with the relevant clinical (either therapeutical or prophylactic) applications, that SF68 strain of Enterococcus faecium shows the capability of regularly inhibiting, by means of the production of biologically active substances, with a
20 reproducibility of 100%, the growth of other vancomycin-resistant (VRE) strains of Enterococcus faecium of Van-A and Van-B types, against which it was tested.

The same type of activity can be expected
25 according to the present invention also for the other strains of Enterococcus faecium having similar activity to SF68 strain.

The microbiological studies were carried out according to the proper microbiologic methods.

30 The cultivation of Enterococcus faecium strains

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was carried out in Mueller-Hinton II. broth, overnight at 37°C under a 5% CO₂ atmosphere. The culture of bacteriocins producer SF68 strain was centrifuged at 13,000 rpm during 5 minutes in order to remove the cells, and the cell-free supernatant was then incubated at 80°C during 1 minute (most bacteriocins survive this treatment which allows the operators to prevent producer cells from further growing). The observations at time points "0", "4", "8" and "30" hours were carried out on microtitration plates, to which the following media had been added:

- in the experimental wells, 100 µl of supernatant of studied product and 200 µl of inoculated indicator medium;
- in the control wells, 100 µl of only medium of studied product and 200 µl of inoculated indicator medium;
- in the blank wells, 100 µl of the only medium of the studied product and 200 µl of indicator medium without any inoculum.

The results were expressed as percent inhibition rates according to the following equation ("OD" = "optical densities):

$$\frac{\text{"OD" of control wells} - \text{"OD" of test wells}}{\text{"OD" of control wells} - \text{"OD" of blank wells}} \times 100$$

The strains of Enterococcus faecium showing characteristics of resistance to vancomycin (either of Van-A or Van-B type) against which the

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antibacterial activity of Enterococcus faecium SF68 strain was tested had been isolated in human clinic from different sources (comprising faeces, blood, infected wounds) on the occasion of a multicentric epidemiological study carried out in Belgium. The "Van" genotype was determined by using a "PCR" based on the technique described by Dutka-Malen et al. ("Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci" - J. Clin. Microbiol. 33: 24-27 - 1995). Other strains of Enterococcus faecium came from collections (LGM -- see following table).

The genetic identification of enterococci found in the wells or faecal isolates (see clinical studies mentioned in the following) was carried out by means of the "random amplified polymorphic DNA (RAPD) typing" and by comparing the DNA profiles with those obtained from Enterococcus faecium SF68 strain.

The results obtained from the tests on in vitro activity of SF68 strain as compared to other Enterococcus faecium strains, nearly all from clinic isolation from human subjects, i.e., vancomycin-resistant strains of Van-A type, among which one Iowa 1 strain, and vancomycin-resistant strains of Van-B type (one Iowa 2 strain), and some strains from collections, are reported in the following table:

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Inhibition of various <u>E.faecium</u> strains by E.faecium SF68	No. of tested strains	No. of inhibited strains	Percent inhibition rate by SF68
Vancomycin-resistant	9	9	100%
Van-A type	8	8	100%
Van-B type	1	1	100%
Strains from collections (LMG)	4	4	100%
Totals	13	13	100%

Further tests demonstrated that the observed effect is of bactericidal type in at least 50% of performed test. It is also important to remind that the reproducibility of these results was of 100%.

5 These results are at all surprising and allow us to think that SF68 strain may produce bacteriocins (or other biological products) which are specifically active against not only several pathogenic and enteropathogenic germs in specific
10 way (and also against enteropathogenic viruses), but also against germs of the same Enterococcus faecium species displaying characteristics of resistance to vancomycin, of Van-A and Van-B types.

15 The tests performed are considerably interesting and are very encouraging because they suggest a potential use of Enterococcus faecium SF68 strain (or of other Enterococcus faecium strains having similar biological characteristics) to eradicate from intestines vancomycin-resistant
20 enterococci strains (VRE) and thus purge also bearers of such germs on the occasion of nosocomial

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infections.

Based on the tests performed in vitro, we regarded planning an ample placebo-controlled clinic study to be performed under double-blind conditions and having the purpose of verifying whether a treatment with SF68 is actually capable of removing the presence of VRE's ("vancomycin-resistant enterococci") from the faeces of bearer subject susceptible of contracting the intestinal infection and/or diffusing such strains responsible for nosocomial infections, as being extremely important.

Such a study, by now in course, was preceded by a pilot study on a very limited number of subjects, suitable for obtaining preliminary data and results useful for performing the ample research mentioned above.

This clinical pilot study was performed on 4 volunteers (students) submitted to coprocultural examination within the scope of an epidemiological control program, and in which the presence had been demonstrated of an Enterococcus faecium with vancomycin resistance of Van-A type, with a relatively weakly symptomatic enteritic pattern.

The subjects were treated with a pharmaceutical preparation in the form of capsules containing at least 75×10^6 CFU of Enterococcus faecium SF68® strain per each capsule (available under the trade name BIOFLORIN®), administered at the dosage of 2 capsules three times per day during 5 days.

The control coprocultures were performed at

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time "0", then after the 5 treatment days and were then repeated after 1, 3, 5, and 25 days from treatment end.

After the five treatment days and during the five following days after the treatment end, the presence of Enterococcus faecium SF68 strain in the faeces was detected in all cases, and in 2 cases from 4 the presence was detected also in the control test performed after 25 days after the treatment end.

However, the most important fact is that, in all cases, from control assays performed at treatment end, it was no longer possible demonstrating the presence of Enterococcus faecium strains with vancomycin resistance of Van-A type.

The discrimination between the different strains of Enterococcus faecium (SF68 and VRE) was made possible by the "PCR fingerprinting" methods; the genetic identification of enterococci found in faecal isolates was performed by means of the "random amplified polymorphic DNA (RAPD) typing" and the comparison of the DNA profiles obtained to the DNA profiles obtained from Enterococcus faecium SF68 strain and other isolated VRE's as assignment criteria.

The results from pilot study evidently conferred considerable importance to the extended research into the possibility of eradicating VRE infections by using microbiological agents of Enterococcus faecium SF68 strain, research which is

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by now in course.

As regards the dosages which can be proposed with reference to these particular applications, it should be stated in detail that the strains of

5 Enterococcus faecium must display vital characteristics and the CFU ("colony forming unit") amount to be administered every day must range from 10,000,000 units up to more than 10,000,000,000 units; the width of the dosage range is justified by

10 the matter of fact that the essential aspect for the biological effect is that conditions exist in the body which allow the bacteria to multiply -- which, per se, typically multiply very rapidly (doubling in number every 19 minutes).

15 In order to better understand the features of the present invention, some exemplifying embodiments thereof are reported in the following, relating to the pharmaceutical forms to be used for the purposes of the invention.

20 Such examples have only illustrative, non-limitative purpose.

Examples

The pharmaceutical forms with Enterococcus faecium SF68 strain, to which the present patent

25 relates, are all those which are normally useable for clinic use.

In particular, as compositions, the following examples may be cited:

1) Hard gelatine capsules

30 Per each capsule:

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- Enterococcus faecium SF68 strain ≥75,000,000
- Magnesium stearate 5,5 mg
- Precipitated silica 0,8 mg
- Lactose 257,7 mg

2) Powder in vial with metering spoon

Per 100g of powder:

- Enterococcus faecium SF68 strain ≥7,500,000,000
- Dextrose 75 g
- Dextrin 25 g

3) Granular form in bag

Per each bag of 1 g:

- Enterococcus faecium SF68 strain ≥75,000,000
- Mannitol 150 mg
- Sodium saccharine 10 mg
- Xantan gum 100 mg
- Natural flavour 40 mg
- Sorbitol q.s. up to 1500 mg

5 4) Pellets in bag

Per each bag of 1,2 g:

- Enterococcus faecium SF68 strain ≥75,000,000
- Lactose 120 mg
- Sucrose 702 mg
- Starch 78 mg
- Methylcellulose 200 mg
- Polyvinylpyrrolidone 60 mg
- Natural flavour 40 mg

5) Pellets in capsules

Per each capsule with a content of 380 mg:

- Enterococcus faecium SF68 strain >75,000,000
- Lactose 38 mg

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- Sucrose	257 mg
- Starch	64,25 mg
- Polyvinylpyrrolidone	18,75
- Magnesium stearate	2 mg

The pellets can be made gastroresistant by coating them with a shell of methacrylic acid polymers.

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C l a i m s

1. Use of an Enterococcus faecium of SF68 strain, or having a similar activity, for preparing a medicinal product suitable for therapeutical
5 treatment of infections due to Enterococcus faecium strains resistant to antibiotics and, in particular, to vancomycin (VRE).

2. Use according to claim 1, characterized in that said Enterococcus faecium belongs to SF68
10 strain.

3. Use according to claim 1, characterized in that the infections are specifically intestinal infections, as enteritides and enterocolites.

4. Use according to claim 1, characterized in
15 that it relates to the state of bearer of said vancomycin resistant enterococci (VRE) by apparently healthy subjects, and consequently to the eradication of nosocomial or non-nosocomial epidemic focuses and to the prevention of the diffusion of
20 intestinal or systemic infections by purging the subjects in the bearer state.

5. Pharmaceutical composition for the therapeutical treatment of infections due to Enterococcus faecium strains which are resistant to
25 antibiotics and in particular to vancomycin (VRE), characterized in that, as its active principle, it contains an Enterococcus faecium of SF68 strain, or with similar activity.



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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR BIOLOGICAL TREATMENT OF INFECTIONS BY ENTEROCOCCUS FAECIUM STRAINS RESISTANT TO ANTIBIOTICS AND TO VANCOMYCIN IN PARTICULAR (VRE) (57) Abstract <p>The present invention relates to the use of an <i>Enterococcus faecium</i> strain for preparing a medicinal product suitable for the therapeutical treatment of infections, with particular reference to enterocolites, supported by <i>Enterococcus faecium</i> strains resistant to antibiotics and in particular, vancomycin, the so-said "VRE" strains. In particular, <i>Enterococcus faecium</i> is taken into consideration and disclosed which belongs to that strain referred to as "SF68". The invention also discloses and relates to pharmaceutical compositions for such a use.</p>		

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 8721 Derwent Publications Ltd., London, GB; Class B05, AN 87-145571 XP002035793 & IT 1 112 479 B (GIULIANI SA) , 13 January 1986 cited in the application see abstract</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/-</p>	1-5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>REVUE MEDICALE DE LA SUISSE ROMANDE, vol. 114, no. 7, July 1994, pages 651-654, XP000674785 EDOUARD LOISEAU: "PLACE DE L'ENTÉROCOQUE SF 68 DANS LA PRÉVENTION ET LE TRAITEMENT DES GASTRO-ENTÉRITES INFECTIEUSES ET LIÉES AUX ANTIBIOTIQUES" cited in the application see the whole document</p> <p style="text-align: center;">---</p>	1-5
X	<p>GASTROENTEROLOGY, vol. 99, no. 4, October 1990, pages 1149-1152, XP000670317 MITRA A K ET AL: "A DOUBLE-BLIND, CONTROLLED TRIAL OF BIOFLORIN (STREPTOCOCCUS FAECIUM SF68) IN ADULTS WITH ACUTE DIARRHEA DUE TO VIBRIO CHOLERAE AND ENTEROTOXIGENIC ESCHERICHIA COLI" see the whole document</p> <p style="text-align: center;">---</p>	1-5
X,P	<p>MICROBIAL DRUG RESISTANCE, vol. 2, no. 4, 1996, pages 415-421, XP000674789 LISA L. DENVER ET AL.: "PERSISTENCE OF VANCOMYCIN-RESISTANT ENTEROCOCCUS FAECIUM GASTROINTESTINAL TRACT COLONIZATION IN ANTIBIOTIC-TREATED MICE" see the whole document</p> <p style="text-align: center;">---</p>	1-5
A	<p>EP 0 405 569 A (CERNITIN SA) 2 January 1991</p> <p style="text-align: center;">-----</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

I: ational Application No

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Patent document
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